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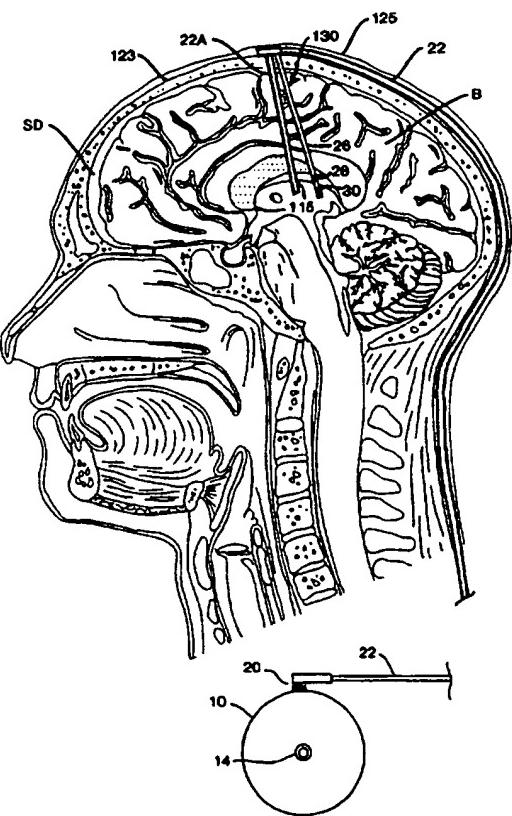
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(54) Title: TECHNIQUES OF TREATING NEURODEGENERATIVE DISORDERS BY BRAIN INFUSION

(57) Abstract

Techniques for infusing drugs into the brain to treat neurodegenerative disorders by means of an implantable pump and catheter. The drugs are capable of altering the level of excitation of neurons in the brain. A sensor is used to detect an attribute of the nervous system which reflects the hyperexcitation of the nerve cells projecting onto the degenerating nerve cells. A microprocessor algorithm analyzes the output from the sensor in order to regulate the amount of drug delivered to the brain.



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TECHNIQUES OF TREATING NEURODEGENERATIVE DISORDERS BY BRAIN INFUSION

Field of the Invention

5 This invention relates to brain infusion techniques, and more particularly relates to such techniques for treating neurodegenerative disorders.

Description of Related Art

10 Neuroscientists have recognized and continue to explore excitotoxicity, a phenomenon referring to excessive excitation of nerve cells leading to degeneration of the nervous system. This phenomena has been used to explain cell loss after stroke or some other hypoxic event. The research has focused on nerve cells that have glutamate neurotransmitter receptors especially susceptible to the sustained insult. Hyperexcitation of these nerve cells is fundamental to the mechanism (Rothman, S.M., Olney, J.W. (1987) *Trends Neurosci.* 10, 299-302). Researchers have also 15 used excitotoxicity to explain the observed cell loss in the CA1 region of the Horn of Ammon in the dentate gyrus of hippocampus in patients and animal subjects that have suffered from seizure activity. Seizures can be viewed as a form of abnormal over excitation of the nerve cells in this region.

20 Typically, neuroscientists have focused on nerve cells that use the transmitter substance glutamate to communicate with target nerve cells; however, other excitatory amino acids (EAA) are included. When nerve cells are abnormally active, experiencing excessive action potentials, they are believed to release excessive amounts of glutamate or other EAA at their synaptic terminals. The presence of 25 excessive amounts of glutamate leads to toxic effects on the secondary nerve cells targeted by the hyperactive ones. These toxic effects are believed to be mediated by an accumulation of calcium.

Benabid et al. (*The Lancet*, Vol 337:Feb 16, 1991, pp 403-406) has shown that stimulation of the Vim nucleus of the Thalamus will block tremor. In this instance, stimulation at frequencies around 100 to 185 pulses per second accomplishes

the same physiological response as a lesion of this region. Thus, it appears that stimulation inhibits the output of these cells. Benabid's research team has extended this work to stimulation of the subthalamus ("Vim and STN Stimulation in Parkinson's disease", *Movement Disorders*, Vol. 9, Supplement 1 (1994); "Effect on 5 Parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation", *The Lancet*, Vol 345, January 14, 1995.

Parkinson's disease is the result of degeneration of the substantia nigra pars compacta. The cells of subthalamus have been shown to use glutamate as the neurotransmitter effecting communication with their target cells of the basal ganglia. 10 The state of hyperexcitation that exists in Parkinson's disease will cause an excessive release of glutamate. This, in theory, will lead to further degeneration via the mechanism described above.

Benabid has proposed a method of arresting degeneration of the substantia nigra by high frequency electrical pulsing of the subthalamic nucleus to block 15 stimulation of the subthalamic nucleus, thereby inhibiting excessive release of glutamate at the terminal ends of the axons projecting from the subthalamic nucleus to the substantia nigra.

Amotrophic Lateral Sclerosis (ALS), sometimes referred to as Lou Gerhig's disease, is a progressive neurodegenerative disease affecting the voluntary motor 20 system. The degeneration of the spinal cord and cortical motor neurons results in paralysis, respiratory depression and death. Glutamate neurons appear to be overactive in this disease state and are suspected of causing the neurodegeneration (S. H. Apel, "Excitotoxic neuronal cell death in amyotrophic lateral sclerosis", TINS, Vol. 16, No. 1, 1993).

Huntington's disease is a degenerative disorder characterized by choreathetosis 25 which is at first slight. Usually, the choreathetosis is accompanied by hypotonus. The motor dysfunction may be accompanied by subtle forms of mental disorder that progress to a deterioration of cognitive function.

SUMMARY OF THE INVENTION

A preferred form of the invention can treat a neurodegenerative disorder, such as Parkinson's disease Huntington's or Amyotrophic Lateral Sclerosis (ALS) , by means of an implantable pump and a catheter having a proximal end coupled to the pump and having a discharge portion for infusing therapeutic dosages of the one or more drugs capable of altering the level of excitation of neurons of the brain. The catheter is implanted in the brain so that the discharge portion lies adjacent to a predetermined infusion site in the basal ganglia or thalamus of the brain.

Alternatively, the catheter may be implanted in a ventricle of the brain or subdurally so that the discharge portion lies within the cerebral spinal fluid (CSF). The pump is operated to discharge a predetermined dosage of the one or more drugs through the discharge portion of the catheter into the infusion site. By using the foregoing method, the neurodegeneration that occurs in diseases, such as Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis, can be alleviated or prevented.

According to one embodiment of the invention, one or more drugs can decrease excitement of the subthalamus or increase inhibition of the subthalamus. According to another embodiment of the invention, the one or more drugs can increase excitement of the thalamus or decrease inhibition of the thalamus.

Another form of the invention uses a sensor in combination with the implantable pump and catheter to administer one or more drugs capable of altering the level of excitation of neurons of the brain to treat a neurodegenerative disorder. In this form of the invention, the sensor generates a signal relating to an attribute of the nervous system which reflects the hyperexcitation of the neurons related to the degenerating neurons. Control means responsive to the sensor signal regulate the therapeutic dosage. For example, the dosage can be increased in response to an

increase in the hyperexcitation of the neurons and is decreased in response to a decrease in the hyperexcitation of the neurons

By using the foregoing techniques, neurodegeneration can be controlled to a degree unattainable by prior art methods or apparatus.

5

BRIEF DESCRIPTION OF THE DRAWINGS

These and other advantages and features of the invention will become apparent upon reading the following detailed description and referring to the accompanying drawings in which like numbers refer to like parts throughout and in which:

10

Figure 1 is a diagrammatic illustration of a portion of the nervous system of the human body in which a preferred form of hyperexcitation sensor, pump and catheter have been implanted;

Figure 2 is a schematic block diagram of a sensor and analog to digital converter circuit used in the preferred embodiment of the invention; and

15

Figure 4 is a flow chart illustrating a preferred form of a microprocessor program for utilizing the sensor to control the dosage of drug administered to the brain.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

20

Referring to Figure 1, a system or device 10 made in accordance with the preferred embodiment may be implanted below the skin of a patient. The device has a port 14 into which a hypodermic needle can be inserted through the skin to inject a quantity of a liquid agent, such as a medication or drug. The liquid agent is delivered from device 10 through a catheter port 20 into a catheter 22. Catheter 22 is positioned to deliver the agent to specific infusion sites in a brain (B). Device 10 may take the form of the like-numbered device shown in U.S. Patent No. 4,692,147 (Duggan), assigned to Medtronic, Inc., Minneapolis, Minnesota, which is incorporated by reference.

25

The distal end of catheter 22 terminates in a cylindrical hollow tube 22A having a distal end 115 implanted into a portion of the basal ganglia of the brain by

conventional stereotactic surgical techniques. Additional details about end 115 may be obtained from pending U.S. Application serial No. 08/430,960 entitled "Intraparenchymal Infusion Catheter System," filed April 28, 1995 in the name of Dennis Elsberry et al. and assigned to the same assignee as the present application.

5 Tube 22A is surgically implanted through a hole in the skull 123 and catheter 22 is implanted between the skull and the scalp 125 as shown in Figure 1. Catheter 22 is joined to implanted device 10 in the manner shown. Device 10 is implanted in a human body in a subcutaneous pocket located in the chest below the clavicle. Alternatively, device 10 may be implanted in the abdomen.

10 In a second embodiment, distal end 115 of cylindrical hollow tube 22A may be implanted in a ventricle. Alternatively, the distal tip may be located beneath the dura under the skull 123 but outside the brain B.

15 Catheter 22 may be divided into twin tubes 22A and 22B (not shown) that are implanted into the brain bilaterally. Alternatively, tube 22B (not shown) implanted on the other side of the brain may be supplied with drugs from a separate catheter and pump.

A sensor 130 is implanted into a portion of a patient's central nervous system.

20 As shown in Figure 1, sensor 130 comprises a sensing lead 26 having two sensing electrodes 28 and 30 located in the subthalamic region, substantia nigra or other brain region whose electrical activity indicates the activity of the degenerating neurons, i.e., the neurons exhibiting hyperexcitation. Alternatively, electrodes 28 and 30 could be carried by lead 22A. Electrodes 28 and 30 are connected to an analog to digital converter 140 (Figure 2) by conductors 134 and 135 which are located within cable 22. The potentials sensed by electrodes 28 and 30 indicate the electrical activity in the subthalamic nucleus and consequently the substantia nigra. Electrodes 28 and 30 transmit a signal related to the excitation of the portion of the brain exhibiting hyperexcitation. More specifically, electrodes 28 and 30 sense an attribute of the nervous system which indicates the hyperexcitation of the nerve cells projecting onto

the degenerating nerve cells or the hyperexcitation of the degenerating nerve cells.. Sensor 130 may take the form of a device capable of detecting nerve cell electrical activity that is related to the hyperexcitation. Such a sensor may be located deep in the brain. For such detecting, sensor 130 may take the form of an electrode inserted into one of the nuclei of the basal ganglia, the thalamus, the internal capsule or the cortex of the brain. Alternatively, such a sensor may be located outside the dura in the bone of the cranium. Signals that are received by the sensor may be amplified before transmission to circuitry contained within device 10.

Alternatively, sensor 130 may electronically transduce the concentration of a transmitter substance infused into the brain or released endogenously. A paper describing such a sensor is entitled "Multichannel Semiconductor-based Electrodes for In Vivo Electrochemical and Electrophysiological Studies in Rat CNS", by van Horne et al., 120 Neuroscience Letters 249-252 (Elsevier Scientific Publishers Ireland Ltd. 1990).

Referring to Figure 2, the output of sensor 130 is coupled by a cable 132 comprising conductors 134 and 135 to the input of analog to digital converter 140. The output of the analog to digital converter is connected to terminals EF2 BAR and EF3 BAR shown in Figure 11A of U.S. Patent No. 4,692,147 ("'147 Patent"). Before converter 140 is connected to the terminals, the demodulator 101 currently shown in Figure 11A would be disconnected.

The present invention may be implemented by providing seven different drug dosages from 0 dosage to a 1.0ml dosage with 0.1ml increments between choices. The time interval between dosages can be selected between one and twelve hours in seven choices. This is the same type of dosage and interval described in connection with device 10 shown in the '147 Patent (column 5, beginning at line 63). The seven drug dosages and corresponding time increments may be loaded into RAM 102a (Figure 11B) of the '147 Patent. The appropriate drug dosage and interval is selected

by a computer algorithm that reads the output of converter 140 and makes the appropriate selection.

One exemplary computer algorithm is shown in Figure 4. Microprocessor 100 included within device 10 reads converter 140 in step 150, and stores one or more values in RAM 102a in step 152. One of seven dosages is selected in step 154, and an appropriate time interval is selected in step 156. The selected dosage and interval of a drug is then delivered through catheter 22 and tube 22A to the basal ganglia of the brain by the pump of the type as described in the '147 Patent.

For some types of sensor, a microprocessor and analog to digital converter will not be necessary. The output from sensor 130 can be filtered by an appropriate electronic filter in order to provide a control signal for a pump of the type shown in the '147 Patent.

The type of drugs administered by device 10 into the brain depend on the specific location at which distal end 115 of tube 22A is surgically implanted. The appropriate drugs for use in connection with the portion of the basal ganglia or thalamus in which tube 22A terminates, together with the effect of the drug on that portion of the brain for reducing the hyperexcitation of the subthalamic nucleus for the purpose of treating Parkinson's degeneration is provided in the following Table I:

TABLE I

EFFECT	PORTION OF BRAIN	DRUG
INCREASE EXCITATION	VL THALAMUS	glutamate agonist
DECREASE INHIBITION	VL THALAMUS	GABA antagonist
INCREASE INHIBITION	GPi/SNr	GABA agonist

EFFECT	PORTION OF BRAIN	DRUG
INCREASE EXCITATION	VL THALAMUS	glutamate agonist
DECREASE EXCITATION	GPI/SNr	Glutamate antagonist
INCREASE INHIBITION	STN	GABA agonist
DECREASE EXCITATION	STN	Glutamate antagonist
INCREASE EXCITATION	GPe	glutamate agonist
DECREASE INHIBITION	GPe	GABA antagonist
INCREASE DOPAMINE	NEOSTRIATUM	Dopamine agonist

In the foregoing Table I, VL Thalamus means ventrolateral thalamus; GPI means internal segment of globus pallidus; SNr means substantia nigra pars reticulata, STN means subthalamic nucleus; and GPe means external segment of globus pallidus.

5

Alternative targets and infusion strategies are appropriate for treatment of degenerative disorders that are hyperkinetic in nature. For treatment of amyotrophic lateral sclerosis appropriate drugs for use in connection with the portion of the spinal cord, cerebral motor cortex, basal ganglia, and thalamus in which tube 22A

terminates, together with the effect of the drug on that portion of the nervous system for decreasing excitation of the thalamic pathway is provided in Table II.

TABLE II

EFFECT	TARGET STRUCTURE	DRUG
DECREASE EXCITATION	MOTOR CORTEX	GLUTAMATE ANTAGONIST
DECREASE EXCITATION	SPINAL CORD ANTERIOR HORN	PKC INHIBITOR
DECREASE EXCITATION	SPINAL CORD ANTERIOR HORN	GLUTAMATE ANTAGONIST
DECREASE EXCITATION	VL THALAMUS	GLUTAMATE ANTAGONIST
INCREASE INHIBITION	VL THALAMUS	GABA AGONIST
DECREASE INHIBITION	GPi/SNr	GABA ANTAGONIST
INCREASE EXCITATION	GPi/SNr	GLUTAMATE AGONIST
DECREASE INHIBITION	STN	GABA ANTAGONIST
INCREASE EXCITATION	STN	GLUTAMATE AGONIST
DECREASE EXCITATION	Gpe	GLUTAMATE ANTAGONIST
INCREASE INHIBITION	Gpe	GABA AGONIST
DECREASE	NEOSTRIATUM	DOPAMINE

DOPAMINE		ANTAGONIST
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Stereotaxic coordinates based on a normal brain for the portions of the brain described in Table I and II are identified in the following Table III:

TABLE III

BRAIN REGION	MEDIAL-LATERAL DIMENSION	DORSAL-VENTRAL DIMENSION	ANTERIOR-POSTERIOR DIMENSION
VL Thalamus	0.7 to 1.8	1.5 to -0.2	0.0 to -1.0
Gpi	0.5 to 2.0	0.5 to -0.7	0.7 to 2.0
SNr	0.5 to 1.5	-0.6 to -1.5	0.7 to -0.7
STN	0.5 to 2.0	0.0 to -1.0	0.6 to -1.0
GPe	1.6 to 2.7	1.0 to -1.0	2.0 to -1.0
Striatum: Caudate Putamen	0.5 to 2.0 1.2 to 3.3	1.5 to 3.0 1.5 to -1.0	1.5 to 3.0 2.5 to -1.2

5

In the foregoing table: the medial-lateral dimensions are relative to midline of the brain; the anterior-posterior dimensions are relative to the midpoint between the anterior commissure and posterior commissure with negative indicating the posterior direction; the dorsal-ventral dimensions are relative to a line connecting the midpoints of the anterior and posterior commissures with negative being ventral to said line; all dimension are in centimeters.

10

Preferred ranges of dosages and specific drugs for the brain infusion sites identified in Tables I are provided in the following Table III:

TABLE III

DRUG CLASS	SPECIFIC DRUG	DOSING RANGE
Glutamate Agonist	D-Cycloserine	1-10 muM
	L-AP4	1-10 muM
	Carboxyphenylglycine	10-500 muM
	L-glutamic acid	1-100 muM
	cis-Piperidine-2,3-dicarboxylic acid	1-10 muM
	(+/-)-trans-ACPD	1-10 muM
	L-APS	1-10 muM
Glutamate Antagonists	MK801(dizocilpine)	1-20 muM
	ketamine Hcl	5-50muM
	AP-3	1-10 muM
	Dextromethorphan	1-100 muM
	MCPD	0.02-10 muM
	dextrorphan tartrate	1-100 muM
	CNQX	1-100 muM
GABA Agonists	baclofen	0.1-10 muM
	muscimol HBr	100-500 muM
GABA Antagonists	Gabazine	1-50 muM

DRUG CLASS	SPECIFIC DRUG	DOSING RANGE
	Saclofen	0.5-25 muM
	Bicuulline	1-100 muM
	picrotoxin	10-100 muM
Dopamine Antagonist	(+) apomorphine Hcl	5-20 muM
	spiperone Hcl	0.1-10 muM
	haloperidol	10-100 muM
	(-) Sulpiride	0.05-1 muM
Dopamine Agonist	methanesulfonate	1-10 muM
	(-) apomorphine pergolide	10-30 muM
Anesthetic	Lidocaine hydrochloride	5-20 muM

In the preceding table, muM means micromolar.

Alternatively, these agents might be infused into the lateral ventricle or third ventricle of the brain or just beneath the dura above the cortex or in the intrathecal space. In this instance the drug would diffuse to the appropriate site of action.

Microprocessor 100 within device 10 can be programmed so that a controlled amount of drug can be delivered to the specific brain sites described in Table I. Alternatively, sensor 130 can be used with a closed loop feedback system in order to automatically determine the level of drug delivery necessary to alleviate the hyperexcitation as described in connection with Figure 3.

By using the foregoing techniques, neurodegenerative disorders can be controlled in a manner previously unattainable.

Those skilled in that art will recognize that the preferred embodiments may be altered or amended without departing from the true spirit and scope of the invention, as defined in the accompanying claims.

We claim:

1. A system for treating a neurodegenerative disorder resulting in degenerating neurons forming part of a nervous system comprising in combination:

an implantable pump;

5 a catheter having a proximal end coupled to said pump and a discharge portion for infusing into a predetermined infusion site in a brain, a cerebral ventricle, subdural space or intrathecal space a therapeutic dosage of one or more drugs capable of altering the level of excitation of neurons in said brain related to said degenerating neurons;

10 a sensor for generating a signal related to an attribute of said nervous system which indicates the hyperexcitation of said degenerating neurons or of neurons related to said degeneration neurons;

and

15 control means responsive to said sensor signal for regulating said therapeutic dosage.

2. A system, as claimed in claim 1, wherein said sensor comprises means for detecting changes in electromagnetic waves generated by muscle or nerve tissue.

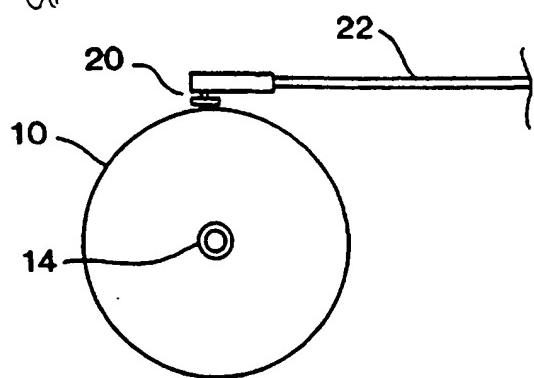
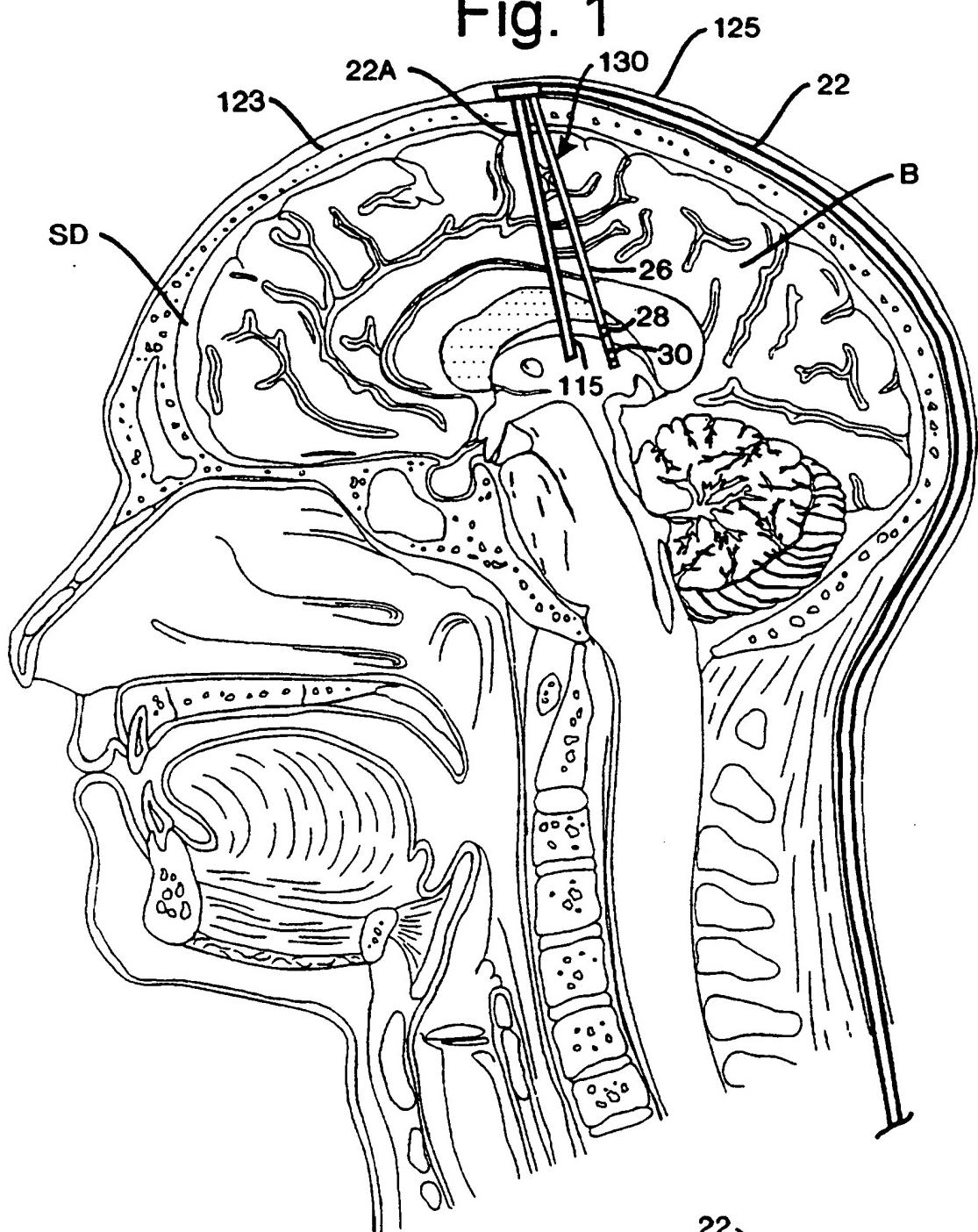
3. A system, as claimed in claim 1, wherein said sensor comprises means for detecting the extent of the hyperexcitation of the glutamatergic neurons of said brain.

20 4. A system, as claimed in claim 1, wherein said control means comprises a microprocessor.

5. A system, as claimed in claim 1, wherein said control means comprises an electrical filter.

25 6. A system, as claimed in claim 1, wherein said control means comprises means for increasing said therapeutic dosage in response to an increase in said hyperexcitation and for decreasing said therapeutic dosage in response to a decrease in said hyperexcitation.

1/2 Fig. 1



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Fig. 2

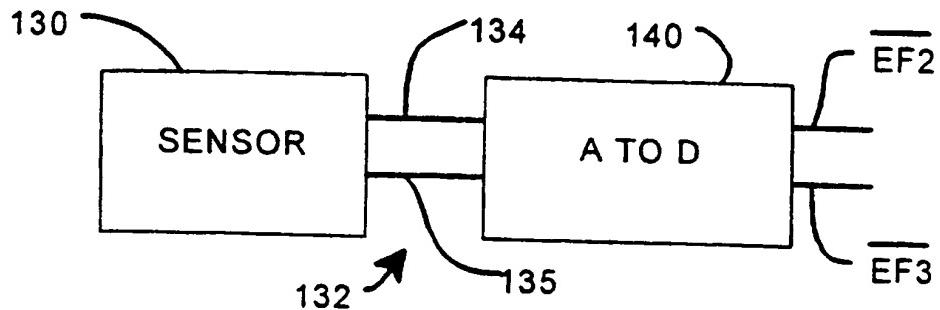
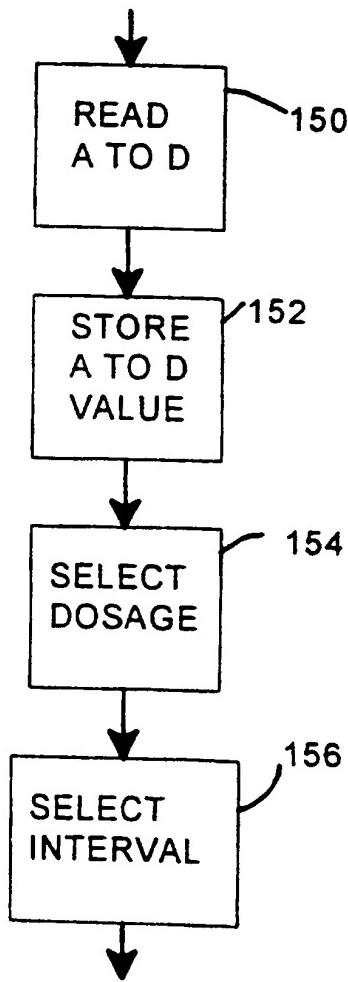


Fig. 3



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/07192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M5/172 A61M5/142

According to International Patent Classification (IPC) or to both national classification and IPC

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Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61M A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 474 547 A (AEBISCHER ET AL.) 12 December 1995 see abstract see column 1, line 18 - column 2, line 15 see column 3, line 41 - line 62 see column 4, line 44 - line 65 see column 6, line 56 - column 7, line 28 see column 9, line 2 - line 50; claim 1 --- EP 0 658 538 A (GENSIA PHARMACEUTICALS, INC.) 21 June 1995 see page 3, line 41 - page 4, line 3 see page 4, line 54 - page 5, line 50 see page 6, line 1 - line 25 see page 8, line 55 - page 9, line 18 see page 10, line 33 - line 38; figures 1,2 --- -/-/	1-6
A		1-6

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/US 97/07192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 617 913 A (BAXTER INTERNATIONAL, INC.) 5 October 1994 see abstract see column 6, line 41 - column 7, line 32; figures 1,2,10,11 ---	1-6
A	US 5 011 472 A (AEBISCHER ET AL.) 30 April 1991 see abstract see column 2, line 34 - column 3, line 61; figures 1,2 ---	1-6
A	US 4 885 002 A (WATANABE ET AL.) 5 December 1989 -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Appl. No.

PCT/US 97/07192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5474547 A	12-12-95	AU 679451 B AU 4689193 A CA 2139324 A EP 0650377 A FI 946125 A JP 7509628 T NO 950112 A WO 9401166 A US 5573528 A AU 632827 B AU 5856590 A CA 2062746 A DE 69001672 T EP 0478671 A ES 2058923 T JP 5500620 T NO 300488 B WO 9015637 A US 5554148 A US 5487739 A US 5106627 A US 5182111 A US 5156844 A	03-07-97 31-01-94 20-01-94 03-05-95 05-01-95 26-10-95 11-01-95 20-01-94 12-11-96 14-01-93 08-01-91 22-12-90 23-12-93 08-04-92 01-11-94 12-02-93 09-06-97 27-12-90 10-09-96 30-01-96 21-04-92 26-01-93 20-10-92
EP 0658538 A	21-06-95	US 5108363 A AT 129644 T AU 634152 B AU 3008889 A DE 68924661 D DE 68924661 T EP 0329464 A ES 2081299 T IE 71651 B JP 2017048 A US 5460605 A US 5395970 A US 5286252 A US 5234404 A	28-04-92 15-11-95 18-02-93 24-08-89 07-12-95 21-03-96 23-08-89 01-03-96 26-02-97 22-01-90 24-10-95 07-03-95 15-02-94 10-08-93
EP 0617913 A	05-10-94	NONE	

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. Application No
PCT/US 97/07192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5011472 A	30-04-91	CA 1332333 A EP 0433341 A WO 9002580 A	11-10-94 26-06-91 22-03-90
US 4885002 A	05-12-89	JP 1683590 C JP 3049452 B JP 63115538 A	31-07-92 29-07-91 20-05-88